REMARKS

Applicant's attorneys ("Applicant") appreciate the examiner's review of the Response filed May 19, 2009. Applicant has carefully reviewed the application in light of the Final Office Action mailed August 7, 2009 by the U.S. Patent and Trademark Office ("the Office"). The following remarks are respectfully submitted to illustrate that the application is in condition for allowance.

By this response, Claims 1, 3, 6, 7, 15, 24 and 26 are amended; claim 11 is cancelled; and claims 41 and 42 are added. No new matter has been added by this Amendment. Support for the claim amendments can be found in at least the claims and the specification, including, for example, at page 12, ll. 6-8, and original Claim 1. As such, Claims 1-10 and 12-42 are pending in the application and submitted for reconsideration.

Further, this response amends the specification to correct an inadvertent typographical error. When filed, the specification contained HG to represent the hydrophobic group. To correct this error, the specification amendment removes HG and replaces it with GH. No new matter has been added by this amendment.

Rejection of claims under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 7 and 24 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite and failing to particularly point out and distinctly claim the subject matter that the applicants regard as the invention. Office Action at pages 4-5. Examiner maintains the rejection of claim 7 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "based on" language which was rejected by the examiner does actually refer to cations that may be obtained directly or indirectly from the compounds (namely from amines, polyamines, polyethyleneimines, amino acids…). Applicant believes that "cations based on amine" is fully understandable to a person skilled in the related art as it simply denotes a chemical entity similar to an amine and having a positive charge, just like an ammonium ion. Examiner further rejects the "narrow and broad limitations within the same claim" 7, where the

Markush group recites "organic cations based on amino acids" and also recites "organic cations based on lysine" and "organic cations based on arginine". Applicant has removed the objectionable species lysine and arginine as being already included in the genera "amino acids."

Nevertheless, to expedite prosecution, Applicant has removed the objectionable language "based on" to clarify the invention and believe that currently amended claim 7 is thus rendered allowable.

Examiner also maintains the rejection of claim 24 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully disagree; however, to expedite prosecution, Applicant has modified claim 24 and added new claims 41 and 42 and believes that currently amended claim 24 is thus rendered allowable.

Rejection of claims under 35 U.S.C. § 112, first paragraph-enablement

The Examiner rejects claims 3 - 7, 9 - 15, 17 - 26 and 35 - 40 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable one of skill in the art to make or use the invention commensurate in scope with the claims. Office Action at page 5.

Specifically, the Examiner alleges that examples of two hydrophobic groups in the specification is insufficient support for numerous genera of structural variants. Applicant respectfully disagrees and believes that the examples mentioned in the specification enable the skilled person to appreciate the full scope of the invention. The expedite prosecution, however, Applicant has amended the claims to limit the hydrophobic groups to α-tocopherol, cholesterol and n-dodecanol.

Examiner states at page 5 of the Office Action that "the only active principle (AP) recited in the claims is an interleukin". Applicant wishes to remind the Examiner that the active principle is not the core element of their invention but "the liquid pharmaceutical formulation for the prolonged release of at least one active principle(s) AP" further comprising "submicronic particles of water-soluble biodegradable polymer PO carrying hydrophobic groups GH",

"wherein the concentration of PO is sufficiently high such that a gelled deposit forms *in vitro* in an aqueous solution comprising bovine serum albumin in a concentration of 30 mg/ml". This value of 30 mg/ml is used to determine the gelling concentration of the polymer PO *in vitro*. It is not a minimum value required to obtain the gelled deposit, as the formation of a gelled deposit depends on the concentration of polymer PO with regard to the concentration of BSA. The specification at page 10, ll 25-29 explains that concentration of PO needs to be greater than 0.9.C1, where C1 is the "*induced gelling*" concentration of the particles of PO. This is shown in particular in Example 6 where the critical concentrations C1 are determined for polymers P1, P3 and P6 in the presence of 30 mg/ml of BSA.

In order for a skilled person to achieve the claimed invention, there is no requirement regarding the nature or concentration of the active principle. The nature of the active principle does not play a role in the gelling of the formulation. Instead the key parameter is a specific concentration of PO.

As mentioned in the instant application, such a formulation gives particularly good results with interleukin but the claimed invention is not limited to one single active principle as many different active principles could be incorporated in the same gelling formulation.

Page 11 of the specification gives further indication regarding the role of the polymer PO that may be "associated or not associated with at least one interleukin and optionally with at least one other AP" in supramolecular arrangements "arbitrarily referred to as "submicronic particles" or "nanoparticles"" (ll 11-13). "[T]hese formulations are liquid, [...] [t]hey only gel in vivo" (ll 16 and 18). As explained at page 10, ll 21-23, "[the] concentration of PO is set at a sufficiently high value to allow the formation of a gelled deposit after parenteral injection, in the presence of at least one protein." Again, these statements demonstrate that the polymer PO is able to gel in the presence of at least one physiological protein, even when not associated with the active principle.

Examiner also states at page 5 of the Office Action that "[t]here is insufficient structural information in the claims or the specification to provide an adequate description of discrete species of the claimed biodegradable polymers." As Applicant notes that on page 6 of the

specification, hydrophobically modified polyamino acids have been well known and described in the art.

Applicant reasserts that there is no undue burden for the person skilled in the art to synthesize such polymers PO in order to associate them to an active principle in the conditions of the claimed invention. Given the basic understanding of chemical synthesis by one of ordinary skill in the art, the specification discloses sufficient detail that any experimentation would not be undue, but merely routine. The specification discloses the properties of the polymers and formulations of the claimed invention and tests to determine if the polymers and formulations have these properties. *See, Id.* at pages 9 - 19. One of skill in the art, therefore, would be able to manufacture a range of formulations and given the teachings of the specification, it would be routine experimentation to determine if the manufactured formulation was within the scope of the claimed invention. Accordingly, the applicants respectfully request the Examiner withdraw the rejection of claims 3-7, 9-15, 17-26 and 35-40 under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement.

Applicant confirms that in claim 7 "m" can be zero and in claim 9 "l" can be zero". These are alternatives where each polyamino acid residue is grafted with an hydrophobic group (m=0) or where no –NH–CH(R^5)–C(=O)– group is present (l=0) in the hydrophobic groups. The alternatives mentioned by the Examiner are in the scope of the present invention and in particular in the scope of claim 7 and claim 9, which pertain to a liquid formulation comprising at least one active principle that is non-covalently associated with the polyamino acid. Applicant believes that no discrete species is required in the description to illustrate the invention, as long as the invention can be understood and reproduced.

Again the Examiner states at page 5 of the Office Action that "[c]laim 11 recites subgenera of hydrophobic groups, but does not otherwise limit the hydrophobic groups to any particular species". Applicant points out that the structure of the hydrophobic group is not relevant to their invention. Indeed the only technical features that need to be considered to achieve the claimed invention are the chemical properties of the hydrophobic groups, namely their hydrophobicity. Moreover, claim 11 is already limited to "alcohol precursor[s]" selected from a limited list of hydrophobic groups "consisting in octanol, dodecanol […], tocopherol and

cholesterol". Applicant respectfully disagrees and believes that the list of hydrophobic groups is proper. However for sake of expedition applicant agrees to limit the scope of their invention to the hydrophobic groups of α-tocopherol, cholesterol and n-dodecanol.

Examiner at page 5 of the Office Action states that "claim 3 [...] recites "at least one active principle"". The applicant wants to point out that claim 3 recites "wherein at least one of the active principle(s) is an interleukin". Claim 23 which depends from claim 3 does actually limit the at least one active principle which is an interleukin to interleukin-2.

Examiner points out at page 6 of the Office Action that "[c]laim 24 recites that the formulation further comprises at least one active principle selected from super-generas that include proteins [...] and it also recites more narrow examples of peptides and mixtures thereof". Claim 24 has been amended and new claims 41 and 42 have been added to address the examiner's objection.

Rejection of claims under 35 U.S.C. § 112, first paragraph – written description

The Examiner rejects claims 3-7, 9-15, 17-26 and 35-40 under 35 U.S.C. § 112, first paragraph, alleging that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the Examiner alleges that because there is insufficient recitation of distinguishing characteristics, the specification does not provide adequate written description for a liquid formulation comprising at least one active principle which is a protein, and a biodegradable polymer with hydrophobic groups. Office Action at page 11.

While Applicant disagrees, to expedite prosecution Applicant has significantly limited the hydrophobic groups to α-tocopherol, cholesterol and n-dodecanol. Further, the claims are limited to "wherein at least one of the active principle(s) is an interleukin." The other limitations of the claims have written description as per 66 Fed. Reg. 1099, 1104 (2001) because one of skill in the art would recognize that the applicant was in possession of the necessary common

attributes or features of the elements possessed by the members of the genus in view of the species disclosed. The claimed invention has the same physical properties as claimed: the ability of forming gelled deposit in an aqueous solution comprising bovine serum albumin in a concentration of 30mg/ml. Applicant therefore requests the rejection be withdrawn.

Rejection of claims under 35 U.S.C. § 103

The Examiner rejects claims 3-7, 9-15, 17-26 and 36-40 under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO00/30618 ("Huille"), U.S. Patent No. 7,030,155 ("Lambert") and U.S. Patent No. 5,102,872 ("Singh") as evidenced by the Handbook of Chemistry and Physics, 88th Ed. 2008 and Akiyoshi. Applicants traverse this rejection.

Currently amended claim 1 is to:

> A liquid pharmaceutical formulation for the prolonged release of at least one active principle(s) (AP),
>
> wherein at least one of the active principle(s) is an interleukin,
>
> wherein said formulation is liquid in the ambient atmosphere and is liquid at physiological temperatures, at physiological pH, in the presence of a physiological electrolyte in a physiological concentration, or in the presence of at least one surfactant,
>
> and wherein said formulation comprises an aqueous colloidal suspension of low viscosity comprising submicronic particles of water - soluble biodegradable polymer PO carrying hydrophobic groups GH selected from the group consisting of α-tocopherol, cholesterol and n-dodecanol, wherein said submicronic particles are non - covalently associated with at least one active principle AP, and wherein the dispersion medium of the aqueous colloidal suspension of low viscosity consists consisting essentially of water, and
>
> wherein the concentration of PO is sufficiently high such that a gelled deposit forms *in vitro* in an aqueous solution comprising bovine serum albumin in a concentration of 30 mg/ml.

Thus, the claim requires an aqueous solution comprising bovine serum albumin ("BSA") in a concentration of 30mg/ml. None of the cited references alone or in combination teach or suggest 30mg/ml, much less render 30mg/ml BSA obvious.

The Examiner states that Huille teaches a solution of 0.5% BSA, but "does not specifically recite a concentration of 30mg/ml." Office Action at page 11. Applicants disagree in that Huille, neither specifically nor indirectly, teaches 30mg/ml. At best, Huille teaches a solution of 0.5% BSA, which is 5 mg/ml. 5mg/ml BSA is not the claimed 30 mg/ml BSA.

Further, Singh does not cure this deficiency. Singh teaches a "microencapsulated composition comprising IL-2 conjugated with a polyoxyethylenes polymer, and mixed with a release-modulating amount of humen [sic] serum albumin." *See*, Singh at Abstract. All embodiments and teachings of Singh therefore teach a combination of three compounds that may be in an injectable formulation:

1) IL-2 conjugated with polyoxyethylenes polymer,
2) human serum albumin ("HSA"; which Examiner alleges is equivalent to BSA), and
3) PLG microcapsules.

See, Id. at Abstract; Col. 4, ll. 19-46; Col. 7, ll. 63-65; Col. 8, ll. 57-59; all Examples; claims. The Examiner relies on Col. 5, l. 59 – Col. 6, l. 5 to show the ratio of PEG-IL-2 to HAS may be 1:5 to about 1:30 by weight, and alleges that the weight ratio is within the recited 30mg/ml.

Applicants disagree, and note that there is still the third component of the formulation: PLG. When PEG-IL-2, HAS and PLG is combined, the resulting dry microcapsules are 1-20% protein (PEG-IL-2 and HAS). *Id.* at Col. 7, l. 63 – Col. 8, l. 3. Thus, even if the PEG-IL-2 was a *di minimus* amount, the dry powder would be a maximum of 20% serum albumin.

It is impossible to prepare a liquid formulation of 30mg/ml serum albumin from a dried composition of 20% albumin. The dried composition must be more than 30% serum albumin before a liquid is added in order to form the claimed 30mg/ml serum albumin. Thus, Singh does not cure the deficiency of Huille.

The Examiner also alleges that it is obvious to optimize the concentration of BSA. Applicants note, however, that one of skill would not increase the BSA concentration to optimize, in view of Huille and/or Singh. Singh teaches that having a higher protein loading level "tend to cause enhanced initial burst release." *Id.* at Col. 7, l. 63-Col. 8, l. 6. Thus, to

prepare a prolonged release formulation, one of ordinary skill would not modify the formulation of Singh to include *more* serum albumin. This is in contrast to the claimed invention, where a liquid formulation of 30mg/ml of BSA instead has prolonged release. *See*, Claim 3.

In addition, Singh teaches that the "formulations of the invention will generally be injectable suspensions of microcapsules, or dry microcapsule compositions suitable for suspension". Singh at Col. 8, ll 34-36. The formulation of claim 3 of the instant application is liquid under the injection conditions and will form a gelled deposit in the presence of a physiological protein such as serum albumin. Singh does simply not teach a gelled deposit obtained in the presence of serum albumin. Huille also does not cure this deficiency and therefore cannot render obvious claim 3 of the instant application.

Lambert also does not cure the deficiency of Huille and/or Singh. The Examiner relies on Lambert to argue that "a person of ordinary skill in the art would have been able to make hydrophobic moieties grafted to proteins or amino acid polymers [...] and the resulting structure and function of the grafted hydrophobic group would have been predictable; to improve solubility of poorly soluble drugs." Office Action at page 12. Applicants note the instant invention does not pertain to the solubility improvement of a drug by way of hydrophobic groups or hydrophobic moieties. The instant invention at claim 3 is to a formulation "wherein the concentration of PO is sufficiently high such that a gelled deposit forms *in vitro* in an aqueous solution comprising bovine serum albumin." As such, Applicants request the Examiner withdraw the rejection.

Furthermore, Akiyoshi et al. does indeed describe the spontaneous dissociation of Insulin from the polymer when BSA is added. This teaching does not help the skilled person to achieve the instant invention. Instead, this teaches away from the instant invention which provides a gelled deposit formed by association of the polyamino acid and the serum albumin and also comprising the protein.

For at least the above reasons, Applicants request the rejection to claim 3 be withdrawn. Claims 4-7, 9-15, 17-26 and 35-40 all depend directly or indirectly upon claim 3, and thus contain at least the same limitations. For this reason, Applicants request these rejections be withdrawn.

OBVIOUSNESS - TYPE DOUBLE PATENTING REJECTIONS

The examiner rejects claims 3-7, 9-15, 18-22, 24, and 36-40, alleging they are obvious over claims 1 to 35 of Huille, as evidenced by the Handbook and Akioyshi. Applicants hereby incorporates the above arguments.

The instant claims are to prolonged release of an active principle, which includes 30mg/ml serum albumin, where a liquid formulation forms a gelled deposit *in vitro*. At best Huille teaches a solution of 0.5% BSA, which is 5 mg/ml. 5mg/ml BSA is not the claimed 30 mg/ml BSA. Further, as noted above Singh also does not teach 30 mg/ml BSA. One desiring to optimize Huille and/or Singh would not increase the serum albumin to 30mg/ml for multiple reasons. First, Singh teaches that increasing the serum albumin would enhance initial burst release. This is in contrast to the claimed invention, where a liquid formulation of 30mg/ml of BSA instead has prolonged release. Second, neither reference teaches a liquid formulation forms a gelled deposit *in vitro*. Thus, one of skill would not form the claimed composition by increasing serum albumin. Therefore, the presently claimed invention cannot be obvious over these references. Applicants therefore respectfully request to this rejection be withdrawn.

The examiner also alleges that claims 3-7, 9-15, 17, and 21-26 are obvious over claims 3-7, 9-15, and 21-26 of the pending US application number 10/580,023 and claims 3-7, 9-15, 17, 21, 22 and 24-26 are obvious over claims 3-7, 9-15, and 21-26 of co-pending US application number 10/580,037. Applicants note that the instant application has a priority date of November 21, 2003. Further, these two application numbers 10/580,023 and 10/580,037 have a priority date of November 21, 2003. These two applications therefore are not available as prior art against the instant application. For this reason, the double patenting rejection cannot be maintained and should be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, the applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Applicant submits concurrently a Request for Continued Examination pursuant to 37 C.F.R. § 1.114. Please charge our Credit Card in the amount of $810.00 covering the fees set forth in 37 C.F.R. § 1.17(e). In the event that any extensions of time are necessary to prevent the abandonment of this patent application, then such extensions of time are petitioned. The U.S. Patent and Trademark Office is authorized to charge any additional fees that may be required in conjunction with this submission to Deposit Account Number 50-2228, referencing matter number 022290.0158PTUS, from which the undersigned is authorized to draw.

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Respectfully submitted,

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